

REMARKS/ARGUMENTS

Applicants' counsel thanks Examiner Lucas for his continued careful and thorough examination of the present application.

Applicant continues to acknowledge that the Examiner has withdrawn the species elections with regard to Fraction A and Fraction C of Quillaja Saponaria Molina and that claims 3, 11, 16, 17, and 19 are withdrawn. Applicant notes again that claims 3 and 11 depend from claims 1 and 9, respectively. Accordingly, on allowance of claims 1 and 9, rejoinder and allowance of the claims 3 and 11 is respectfully requested pursuant to the Office's rejoinder procedure. MPEP § 821.04.

Applicant acknowledges that the Examiner has withdrawn the prior rejection of claims 1, 2, 4-7, and 18 under 35 U.S.C. § 112 for indefiniteness and has withdrawn the prior rejection of claims 1, 2, 6, 7, 8, and 18 under 35 U.S.C. § 102(b) as being anticipated by the Iosef reference (Vaccine 20:1740-53).

Claims 7, 8, 13, 14, 22, and 23 have been amended to more clearly describe the invention, as explained below.

No new matter has been entered. Basis for the amendments can be found in the specification as filed. Regarding claims 7, 8, 13, 14, and 22-23, the application discloses saponins derived from raw extract of Quillaja Saponaria Molina. Paras. [0034]-[0038]. More specifically, the application discloses a raw extract from Quillaja Saponaria Molina and the fractions A, B, C, B3, B4, B4B and QA1-22 thereof. Paras. [0034-0038]. The application also discloses that saponins of the raw extract can be separated into Fraction A and Fraction C, among other fractions. Para. [0035]-[0037]. Such fractions are termed fractions from Quillaja Saponaria Molina. Para. [0038]. Of note, such fractions are also be defined in the art as

fractions of Quil A. This is evident, for example, from the WO 96/11711 reference to Cox, cited in paragraphs [0035] and [0063] of the present application. Specifically, the Cox reference states the following: "[S]aponins with useful adjuvant activity have been derived from the South American tree *Quillaja saponaria* Molina. Saponin from this source was used to isolate a 'homogeneous' fraction denoted 'Quil A' (Dalsgaard, 1974)". WO 96/11711, p. 1, lines 24-27. Moreover, the Cox reference discloses fractions of *Quillaja Saponaria* Molina, specifically termed fractions B4B, B3, and B2 of Quil A. WO 96/11711, p. 3, lines 5-8.

Further regarding claims 22-23, the application discloses that composition MM703 was prepared by mixing Matrix A and Matrix C, wherein Matrix A corresponds to iscom matrix particles including Fraction A of *Quillaja Saponaria* Molina and Matrix C corresponds to iscom matrix particles including Fraction C of *Quillaja Saponaria* Molina. Thus, MM703 comprises a plurality of iscom particles, wherein a first iscom particle includes Fraction A and not Fraction C, and a second iscom particle includes Fraction C and not Fraction A, consistent with claims 22 and 23, as currently amended.

The Examiner has maintained the rejection of claims 8 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner has rejected claims 8 and 14 based on lack of clarity regarding the meaning of "Fractions A or C of *Quillaja saponin* Fraction A." Office action, p. 3. Claims 7 and 13, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprises at least one glycoside fragment from *Quillaja Saponaria* Molina. Claims 8 and 14, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprises at least one of

Fraction A and Fraction C of Quillaja Saponaria Molina. The rejection of claims 8 and 14 is therefore respectfully submitted to be overcome.

The Examiner has rejected claims 22 and 23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner has rejected claims 22 and 23 based on lack of clarity regarding the meaning of “different fractions of Quillaja saponin Fraction A.” Office action, p. 3. Claims 22 and 23, as amended, are directed to a method and a composition, respectively, wherein the iscom particle comprise various fractions of Quillaja Saponaria Molina. For the reasons indicated above regarding amendment of claims 8 and 14, the rejection of claims 22 and 23 is respectfully submitted to be overcome.

The Examiner has also rejected claims 22 and 23 on the basis that it is not clear what is meant by the claim language “wherein a plurality of the iscom particles comprise different Fractions of Quillaja saponin Fraction A.” Specifically, the Examiner has indicated that “[i]t is not clear what is meant by the claim language if the claim is reading on embodiments wherein the plurality of iscoms each have the same saponins which is made up of different fractions of Quil A . . . , or if the claims are drawn to embodiments wherein the plurality of iscom particles comprise a plurality of iscom particle populations, each comprising a different Fraction of Quil A from the other iscom populations.” Office action, p. 4. Claims 22 and 23, as amended, are directed to methods and compositions, respectively, wherein a plurality of the iscom particles comprise a first iscom particle and a second iscom particle, the first iscom particle comprising a first fraction of Quillaja Saponaria Molina and not a second fraction of Quillaja Saponaria Molina, and the second iscom particle comprising the second fraction of Quillaja Saponaria

Molina and not the first fraction of Quillaja Saponaria Molina. The rejection of claims 22 and 23 is therefore respectfully submitted to be overcome.

The Examiner has maintained the rejection of claims 1, 2, 6, 9, 10, and 15 under 35 U.S.C. § 102(b) as being anticipated by Wechter et al., U.S. Pat. No. 6,177,081. Moreover, the Examiner has extended the rejection to claim 21. Specifically, the Examiner maintains, as stated in the previous Office action, that “Wechter teaches live attenuated viruses for use in vaccines,” that “[t]he reference teaches the combination of the attenuated viruses with an iscom,” and that “the reference also inherently teaches claim 6” since “iscoms are known in the art to comprise glycosides and lipids.” Office action dated December 17, 2008, p. 5; Office action dated July 28, 2008, p. 5. Moreover, in response to the Applicant’s assertion that the teachings of Wechter inevitably involve production steps that will kill microorganisms, the Examiner has stated that such an argument is not sufficient where evidence is required. The Examiner has also stated that Applicant’s argument is not consistent with the teachings of Wechter, given that Wechter “specifically indicates that the live viruses can be incorporated into the ISCOMs, and nowhere indicates that the end result would be an inactivated (killed) virus.” Office action dated December 17, 2008. As can be seen, the Examiner has compared the vaccines of Wechter with the compositions and methods as claimed in claims 1, 2, 6, 9, 10, 15, and 21.

Respectfully, as previously asserted by Applicant, now with evidentiary support in the form of a declaration by one of the Inventors, Morein, the two are not the same. Specifically, as previously asserted by Applicant, claim 1, as amended, is directed to a method of preparing an antigenic composition, based on combining an iscom particle and at least one living micro-organism, and claim 9 is directed to a composition comprising at least one iscom particle and at least one living micro-organism. In contrast, as previously asserted by Applicant, Wechter

teaches the use of a live attenuated virus as a starting material for antigen incorporation into an iscom particle, said use inevitably involving production steps that will kill any virus or other micro-organism, and thus Wechter does not teach any composition that includes an iscom particle and a live micro-organism or any method for making such a composition.

More specifically, as indicated by the Inventor Morein, the technology published and used for making iscom particles from whole microorganisms from before 2004, including the technology described by Wechter, is based on extraction of antigens from whole microorganisms followed by incorporation of the antigens into iscom matrix particles to yield iscom particles. Morein Declaration, pp. 3-4. The technology is not based on incorporation of whole organisms per se into iscom particles. Morein Declaration, p. 4. This is because the technology involved solubilization procedures that would necessarily result in killing of any live microorganisms and because microorganisms are generally too large to be incorporated into iscom particles. Morein Declaration, p. 4. Moreover, the Wechter reference indicates that incorporation of live attenuated viruses into iscom matrix particles results in a composition lacking any live viruses, given that Wechter indicates that presentation of viral coat protein antigens in iscom particles, presumably particles resulting from incorporation of live attenuated viruses into iscoms, offers the advantage that no replicating viral nucleic acid is introduced into the host. Morein Declaration, pp. 4-5. This implies that incorporation necessarily results in killing of any live microorganisms.

In view of the factual assertions made by the Inventor in the declaration, it becomes clear that even though the reference to Wechter may indicate that "Live attenuated viruses can . . . be incorporated into immunostimulating complexes (ISCOM) for use as a vaccine using methods well known in the art," the process would involve extracting antigens from the live viruses by

solubilization, followed by incorporation of the antigens, not incorporation of whole microorganisms into iscom matrix to yield iscom particles. Moreover, it becomes clear that the process would inevitably result in killing of the microorganisms, not incorporation of live microorganisms into iscom matrix or iscom particles.

Thus, for at least the foregoing reasons, Wechter fails to teach any composition that includes an iscom particle and a live virus, or any other live micro-organism. In contrast, according to the present invention as claimed in claims 1, 2, 6, 9, 10, 15, and 21, an iscom particle or iscom matrix particle is combined with a live micro-organism in a single composition without incorporation of the live micro-organism into the iscom particle and without killing of the live micro-organism. The rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2 and 6 both depend from claim 1 and claims 10, 15, and 21 depend from claim 9 and accordingly the rejection of these claims is also respectfully submitted to be overcome.

The Examiner has maintained the rejection of claims 1, 2, 5-10, and 13-15 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein et al. (U.S. Pat. No. 5,679,354). The Examiner has also extended the rejection to new claims 20 and 21 on the same grounds and to new claims 22 and 23, assuming that the claims read on embodiments wherein a single population of iscoms comprises more than one Fraction of Quil A, also on the same grounds. Specifically, the Examiner has stated that “[w]hile Wechter teaches the incorporation of attenuated viruses into iscoms, it does not specify the formula of the iscoms.” Office action dated July 28, 2008, p. 7. The Examiner then argued that “Morein provides teachings relating to iscoms for use as an adjuvant for antigens.” Office action dated July 28, 2008, p. 7. Respectfully, as previously argued by Applicant and as now supported by evidence in the form

of a declaration, the incorporation of attenuated viruses into iscoms is not the same as making an antigenic composition by combining an iscom and at least one live micro-organism. Specifically, as indicated above, the technology for incorporation of live attenuated viruses into iscom particles, as described by Wechter, involved solubilization procedures that would necessarily result in killing of any live microorganisms, because microorganisms are generally too large to be incorporated into iscom particles, and because the Wechter reference indicates that incorporation of live attenuated viruses into iscom matrix particles results in a composition lacking any live viruses. Morein Declaration, p. 4. As indicated above, Wechter does not teach any antigenic composition comprising an iscom and at least one live micro-organism. Morein also does not teach such a composition. Morein Declaration, p. 8 (“[W]hen the inventors of the ‘354 patent, including myself, indicated in the ‘354 patent that iscom matrix could be used as an adjuvant with whole organisms, we did not intend that Quillaja saponin and/or iscom matrix/iscom particles would be used with live whole microorganisms.”). Thus, the combination of Wechter and Morein does not make obvious the inventions as claimed in claims 1 and 9. For at least these reasons, the rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2, 5-8, 10, 13-15, and 20-23 depend from claims 1 or 9, either directly or indirectly, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

The Examiner has maintained rejection of claims 7, 8, 13, and 14 under 35 U.S.C. § 103(a) as being unpatentable over Wechter in view of Morein as applied to claims 1, 2, 5, 6, 9, 10, 13, and 15, and further in view of Cox et al. (WO 96/11711). The Examiner has also extended the rejection to new claims 22 and 23. The rejection is impliedly based on an assumption that the combination of Wechter and Morein makes obvious an antigenic

composition comprising an iscom and at least one live micro-organism. Again, as previously argued by Applicant and as now supported by evidence in the form of a declaration, for the reasons indicated above the combination of Wechter and Morein does not make obvious such an antigenic composition. The rejection of claims 7, 13, 22, and 23 is therefore respectfully submitted to be overcome. Moreover, claims 8 and 14 depend from claims 7 and 13, respectfully, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

The Examiner has maintained rejection of claims 1, 2, 4, 9, 10, 12, 15, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel et al. (U.S. Pat. No. 5,925,359). The Examiner has stated that "Van Woensel teaches a composition for the vaccination of pigs comprising live attenuate[d] PRRS viruses" and "that the composition[] may be combined with an adjuvant." Office action dated July 28, 2008, p. 8. The Examiner has also stated that the reference "specifically suggests the incorporation of the live vaccine antigens in iscoms." Office action dated July 28, 2008, p. 8. The Examiner has further stated that "the reference suggests the additional combination of live[] attenuated vaccines with other antigens, including antigenic material (i.e. antigenic molecules) from other pathogens." Office action dated July 28, 2008, p. 8. Respectfully, as is the case with the Wechter reference, Van Woensel does not teach making a composition by combining an iscom particle and at least one live micro-organism, and thus Van Woensel does not make obvious the inventions as claimed in claims 1 and 9.

Specifically, as indicated by the Inventor Morein, although Van Woensel indicates that incorporation of antigens of a live attenuated virus is a possible way of adjuvation, a person of ordinary skill in the art would realize that Van Woensel does not disclose incorporation of a live attenuated virus into an iscom matrix/iscom particle. Morein Declaration, p. 6. This is because

methods used for production of iscom particles from live attenuated microorganisms involve use of solubilization and cause disintegration or damage of the microorganisms and loss of the ability of the microorganisms to replicate, thus killing the microorganisms. Morein Declaration, p. 6. The rejection of claims 1 and 9 is therefore respectfully submitted to be overcome. Moreover, claims 2, 4, 10, 12, 15, and 18 depend from claims 1 or 9, and accordingly the rejection of these claims is also respectfully submitted to be overcome.

The Examiner has maintained rejection of claims 5-8 and 13-14 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel as applied to claims 1, 2, 4, 9, 10, 12, 15, and 18, and further in view of Cox et al (WO 96/11711). The Examiner has also extended the rejection to new claims 20-23. The Examiner has stated that "Van Woensel teaches compositions comprising an attenuated live virus and an iscom" and "that the compositions may comprise additional antigens." Office action dated July 28, 2008, p. 9. The Examiner has also stated that "Cox teaches that iscoms may be in the forms of iscoms comprising the glycosides and lipids identified in the rejected claims" and "that iscom matrices may be used which incorporate an immunogen." Office action dated July 28, 2008, p. 9. Respectfully, as previously argued by the Applicant, now with evidentiary support in the form of the declaration of Inventor Morein, and as indicated above, neither Van Woensel nor Cox teach a composition comprising an iscom particle and at least one live micro-organism. Thus, the combination of Van Woensel and Cox does not make obvious the inventions as claimed in claims 5-8, 13-14 and 20-23. The rejection of claims 5-8, 13-14, and 20-23 is therefore respectfully submitted to be overcome.

Applicant respectfully submits that all of the presently pending claims are allowable for the reasons set forth above and that the application is in a condition for allowance. Applicant further respectfully submits that the arguments made herein are substantially the same as those

made by Applicant in the previous response, now with evidentiary support. Applicant respectfully requests that the amendment to the claims be entered and that the application be allowed.

In the event that there are any questions relating to this amendment or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that the prosecution of this application may be expedited.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-41848.

Respectfully submitted,
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Date: May 18, 2009